Structure

In This Issue

Special Review Collection: The Lipid Perspective

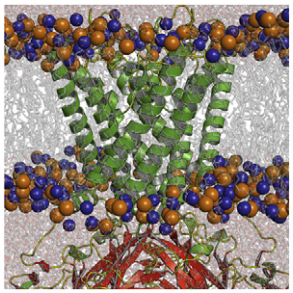
PAGE 1543

Lipids are key ingredients of biological membranes, giving them their basic bilayer structure and thus exerting critical effect on their function. Nonetheless, in order to fully appreciate all aspects of membrane biology, lipid view cannot be divorced from the membrane protein one. In this Perspective, Coskun and Simons focus on the interface of integral transmembrane proteins and membrane lipids in eukaryotic cells, arguing for increased synergy between different fields.

Special Review Collection: Entering the Fourth Dimension

PAGE 1549

Although extremely useful for gaining insight into the overall atomic structure of proteins, crystallography, in most cases, does not offer information on dynamics. One of the methods that can be used in the context of membrane protein structure to add the time dimension into consideration is electron paramagnetic resonance (EPR) spectroscopy, which in conjunction with spin labeling, opens a view into membrane protein dynamics in the native-like environment of a lipid bilayer. Mchaourab and colleagues review the field and highlight the contribution of EPR to membrane protein structural biology.



Special Review Collection: Simulating Membrane Proteins

PAGE 1562

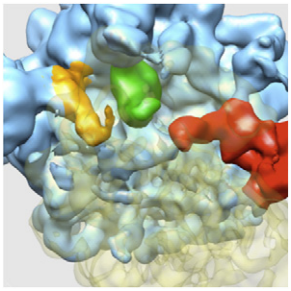
Molecular simulations have been an important tool for investigating membrane protein biology. In this review, Stansfeld and Sansom discuss key improvements to both hardware and simulation methods that have moved the field forward as well as illustrate the range of biological problems that can be tackled in silico, such as transport of solutes by ion channels and signaling by membrane-associated complexes.

Visualizing HIV-1

PAGE 1573

Imaging live cells is an exciting new avenue for cryo-electron tomography (cryo-ET). Jun et al. now establish an advanced approach to correlate time-lapse, live-cell 3D fluorescence microscopy with high resolution cryo-ET and visualize HIV-1 particles at the early stages of infection. This approach connects the dynamic behavior of HIV-1 particles in live cells, allowing insights into temporal and spatial relationship between viruses and host cells.

Conformational States from Cryo-EM Images



PAGE 1582

Single particle cryo-electron microscopy (cryo-EM) is a useful method for investigating structures of macromolecular complexes. Penczek et al. now present a method for resolving conformational heterogeneity within a set of cryo-EM 2D projection images by employing codimensional principal component analysis (PCA). The authors use the method on *T. thermophilus* 70S ribosome to identify four major conformational states and visualize high mobility of the stalk base region.

DNA Damage Signaling System: Mre11 as a Target

PAGE 1591

Mutations of a DNA damage-sensing and -repairing protein, Mre11, are frequently observed in diverse types of human cancers. Park et al. determine the crystal structure of the human Mre11 core and provide insights into understanding the basis of tumorigenic mutations of human Mre11. This structure offers a framework for designing anticancer drugs that target DNA damage signaling system.

Two Sides to StrH Story

PAGE 1603

Streptococcus pneumonia relies on the use of a wide variety of carbohydrate-degrading enzymes for its virulence. StrH is a large β-Nacetylglucosaminidase containing two catalytic modules that work together in the process of degrading N-linked glycans. As discussed by Pluvinage et al., though closely related, the two catalytic modules have subtly different specificities.

Forcing the Point

PAGE 1615

Examining the unfolding of fibrin(ogen), the main component of blood clots, is critical for understanding of the molecular basis of thrombosis. Zhmurov et al. investigate forced unfolding of fibrin(ogen) and resolve the structural underpinnings of this process. The authors uncover that the mechanics of fibrin depends primarily on the globular regions of fibrinogen, with coiled coils playing the role of entropic springs.

Survivin' the Chromosomal Passenger Complex

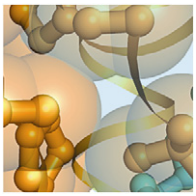
PAGE 1625

The centromeric localization of the chromosomal passenger complex (CPC) is essential for chromosome segregation and is dependent on histone H3 phosphorylation. Jeyaprakash et al. report a crystal structure of the CPC subunit Survivin bound to the histone H3 N-terminal tail phosphorylated at Thr3. The structural analysis identifies putative Survivin-binding epitopes in other mitotic proteins and highlights the specificity determinants.

Structural View of Complement Activation

PAGE 1635

Activation of the complement cascade is triggered upon microbial infection and serves to neutralize pathogens and stimulate the immune response. Here, Gingras et al. determine the structure of the collagen-like domain of mannan-binding lectin bound to its associated serine protease-1 and suggest a general mechanism for the global changes that drive complement activation.



Engineering Glycolipid Transfer Protein

PAGE 1644

Glycolipid transfer protein (GLTP) is a cytosolic protein responsible for transfer of glycolipids between different intracellular membranes. Samygina et al. report structure-guided engineering of human GLTP and produce variants with enhanced transfer selectivity for sufatide (SF) by introducing point mutations at "portal entrance" residues to regulate sphingosine-chain access to the hydrophobic-pocket via a homo-dimerization based mechanism.

In Time for Flu Season

PAGE 1655

Adamantane family antiviral drugs target M2 channel of influenza A and block the proton transport but their effectiveness is greatly compromised by resistance-causing mutations in M2. Here, Pielak et al. report structures of the AM2-BM2 chimeric channel in the absence and presence of bound rimantadine. The structures provide details of small molecule/channel interactions that can serve as the basis for structure-aided drug design to overcome the resistance.

Regulation of Integrin Activation

PAGE 1664

Kindlin-2 belongs to an emerging class of regulators for integrin adhesion receptors. By binding to integrin cytoplasmic face via its C-terminal FERM-like domain, kindlin-2 promotes integrin activation. Perera et al. find that the N terminus of kindlin-2 exhibits a ubiquitin fold and binds to membrane enriched with negatively charged lipids. The data provide significant insight into the mechanism of kindlin-2 regulated integrin activation.

Plagued by Ail

PAGE 1672

Ail is an outer membrane protein (OMP) from *Yersinia pestis* that is highly expressed in bubonic plague. To learn more about how Ail mediates adhesion, Yamashita et al. solve high-resolution crystal structures of Ail, with no ligand bound and in complex with a heparin analog. The work provides a description of how a bacterial OMP uses a multivalent approach to bind host cells.

Opioid Receptor Binding and Activation

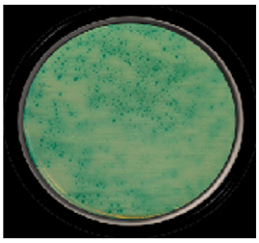
PAGE 1683

Opioids are commonly prescribed and effective painkillers that target the G-protein-coupled receptor, MOR1. Despite its significance, the mechanism of drug binding and receptor activation is not yet fully understood. Serohijos et al. now combine modeling, molecular dynamics simulation, mutagenesis, and ligand binding to show that flexibility of MOR1 intracellular loops increase upon ligand binding, suggesting a potential mechanism for initiating downstream signaling.

Unanticipated Binding Site in Blinkin-BUBR1 Complex

PAGE 1691

BUBR1 is a central component of the mitotic checkpoint, the mechanism that ensures accurate chromosome segregation. The crystal structure of BUBR1 in complex with Blinki, described by Bolanos-Garcia et al. provides molecular details of the recognition mechanism linking mitotic checkpoint signaling with the kinetochore. Disruption of the Blinkin-BUBR1 complex leads to chromosome segregation defects, thus confirming the importance of the interaction for an adequate mitotic checkpoint response.



In This Issue

One Substrate, Multiple Transporter Systems

PAGE 1701

ABC transporters are molecular pumps that transport substrates across cellular membranes. MolA is a bacterial periplasmic binding protein that delivers substrate to an ABC transporter, MolB2C2. Here, Tirado-Lee et al. show that MolA binds molybdate and tungstate. Interestingly, MolA affinity for molybdate is significantly lower than the affinity exhibited by class II ModA binding proteins. The presence of two molybdate loci in *H. influenzae* suggests multiple transport systems for one substrate.

CRIB-PDZ Conformational Switch

PAGE 1711

PDZ domains create protein-protein linkages, typically by binding to a short C-terminal motif. In a few proteins, allosteric regulation of PDZ affinity converts a simple scaffold into a molecular switch. Par-6 assembles a conserved multiprotein complex and regulates cell polarity in response to a GTPase signal. Now, Whitney et al. elucidate the Par-6 conformational switch and provide a mechanistic explanation for transmission of an allosteric PDZ signal.